GIOTRIF®
Afatinib

Composition
1 film-coated tablet contains 40 mg, 30 mg, or 20 mg of afatinib (=free base) corresponding to 59.12 mg, 44.34 mg, or 29.56 mg 2-butenamide, *N*-[4-[3(-chloro-4-fluorophenyl)amino]-7-[[(*3S*)-tetrahydro-3-furanyl]oxy]-6-quinazolinyl]-4-(dimethylamino)-,(*2E*)-, (*2Z*)-2-butenedioate (1:2) (= ***afatinib dimaleate***)

Excipients **:

Tablet Core : lactose monohydrate, microcrystalline cellulose (E460), colloidal anhydrous silica (E551), crospovidone, magnesium stearate (E470b)
Film coating: hypromellose 2910 (E464), macrogol 400, titanium dioxide (E171), talc (E553b), polysorbate 80 (E433), Colourant containing indigo carmine (E132) aluminium hydroxide (only used for 40 mg and 30 mg tablets)

Indications
GIOTRIF® as monotherapy is indicated for the treatment of locally advanced or metastatic non-squamous non-small cell lung carcinoma with adenocarcinoma is predominantly, Epidermal Growth Factor Receptor (EGFR) exon 19 deletions, exon 21 (L858R and L861Q) substitutions, exon 18 (G719X) substitutions, or exon 20 (S768I) substitution mutations, TKI-naïve adult patients.

Limitation of Use:
Safety and efficacy of GIOTRIF have not been established in patients whose tumors have other EGFR mutations.

GIOTRIF as monotherapy is indicated for the treatment of patients with locally advanced or metastatic NSCLC of squamous histology progressing on or after platinum-based chemotherapy.

Dosage and administration

Dosing Considerations
GIOTRIF treatment should be continued until disease progression or until no longer tolerated by the patient (See Table 1).

Patients with renal impairment
Exposure to afatinib was found to be increased in patients with moderate or severe renal impairment (see "Pharmacokinetics"). Adjustment to the starting dose are not necessary in patients with mild or moderate renal impairment. In patients with severe (eGFR 15-29 mL/min) administer GIOTRIF at starting dose of 30 mg once daily. Monitor patients with severe renal impairment and adjust GIOTRIF dose if not tolerated. GIOTRIF treatment in patients with eGFR < 15 mL/min or on dialysis is not recommended.

Patients with hepatic impairment

Adjustment to the starting dose is not recommended in patients with mild or moderate hepatic impairment. GIOTRIF treatment is not recommended in patients with severe (Child-Pugh C) hepatic impairment.

Pediatric population
Treatment of children or adolescents with GIOTRIF is not recommended.

Use of P-glycoprotein (P-gp) inhibitors
Concurrent use of strong P-gp inhibitors or inducers with GIOTRIF should be avoided. If P-gp inhibitors need to be taken, they should be administered simultaneously with or after GIOTRIF.
Patients should be closely monitored for GIOTRIF–related toxicities that may warrant GIOTRIF dose adjustment

Recommended Dose and Dosage Adjustment
The recommended starting dose of GIOTRIF® is 40 mg orally once daily.
Take GIOTRIF on an empty stomach at least 1 hour before or 3 hours after eating. Tablets should be swallowed whole with water.
For patients with emesis, a replacement dose of GIOTRIF is NOT to be taken to make up any potential loss. Take the next dose as scheduled.

Dose adjustment for adverse reactions
Symptomatic adverse drug reactions (e.g. severe/persistent diarrhea or skin related adverse reactions) may be successfully managed by treatment interruption and dose reductions of GIOTRIF as outlined in Table 1.

Table 1 : Dose Adjustment Information for Adverse Reactions

CTCAE[a] Drug Related Adverse Event	Recommended Dosing of GIOTRIF	
Grade 1 or Grade 2	No interruption [b]	No dose adjustment
Prolonged or intolerable Grade 2[c]	Interrupt for up to 14 days until Grade 0/1[b]	Resume with dose reduction by 10 mg decrements [d]
Any Grade ≥ 3	Interrupt for up to 14 days until Grade 0/1[b]	Resume with dose reduction by 10 mg decrements [d]

[a] NCI Common Terminology Criteria for Adverse Events v 3.0
[b] In case of diarrhoea, anti-diarrhoeal medicines (e.g. loperamide) should be taken immediately and continued for persistent diarrhoea until bowel movements cease for 12 hours.
[c] ≥ 48 hours of diarrhoea, ≥ 7 days of nausea and/or vomiting despite anti-emetic treatment, renal impairment (Measured by serum creatinine, newly developed proteinuria, or newly developed decrease in glomerular filtration rate of more than 50%) or ≥ 7 days of other drug-related AEs of CTCAE Grade 2 that are poorly tolerated
[d] If the patient has not recovered to CTCAE Grade ≤ 1 within 14 days or if patient cannot tolerate 20 mg/day, GIOTRIF® should be permanently discontinued.

For Interstitial Lung Disease (ILD) see WARNING AND PRECAUTIONS, Respiratory, Interstitial Lung Disease

Missed Dose

If a dose of GIOTRIF is missed, it should be taken during the same day as soon as the patient remembers. However, if the next scheduled dose is due within 8 hours then the missed dose must be skipped.

Contraindications

GIOTRIF is contraindicated in patients with known hypersensitivity to afatinib or to any of the excipients.

Special warnings and precautions

Assessment of EGFR mutation status
When assessing the EGFR mutation status of a patient, it is important that a well-validated and robust methodology is chosen to avoid false negative or false positive determinations.

Diarrhoea
Diarrhoea, including severe diarrhoea, has been reported during treatment with GIOTRIF (see section Adverse Reactions). Diarrhoea may result in dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. Diarrhoea usually occurred within the first 2 weeks of treatment. Grade 3 diarrhoea most frequently occurred within the first 6 weeks of treatment. Proactive management of diarrhoea including adequate hydration combined with anti-diarrhoeal agents especially within the first 6 weeks of the treatment is important and should start at first signs of diarrhoea. Antidiarrhoeal agents (e.g. loperamide) should be used and if necessary their dose should be escalated to the highest recommended approved dose. Antidiarrhoeal agents should be readily available to the patients so that treatment can be initiated at first signs of diarrhoea and continued until loose bowel movements cease for 12 hours. Patients with severe diarrhoea may require interruption and dose reduction or discontinuation of therapy with GIOTRIF (see section "Dosage and administration"). Patients who become dehydrated may require administration of intravenous electrolytes and fluids.

Skin related adverse events
Rash/acne has been reported in patients treated with GIOTRIF (see section Adverse Reactions). In general, rash manifests as a mild or moderate erythematous and acneiform rash, which may occur or worsen in areas exposed to sun. For patients who are exposed to sun, protective clothing, and/or use of sun screen is advisable. Early intervention (e.g. emollients, antibiotics) of dermatologic reactions can facilitate continuous GIOTRIF treatment.
Patients with prolonged or severe skin reactions may also require temporary interruption of therapy, dose reduction (see section "Dosage and administration"), additional therapeutic intervention, and referral to a specialist with expertise in managing these dermatologic effects. Bullous, blistering and exfoliative skin conditions have been reported including rare cases suggestive of Stevens-Johnson syndrome and toxic epidermal necrolysis. GIOTRIF treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Female gender, lower body weight, and underlying renal impairment
Higher exposure to afatinib has been observed in female patients, patients with lower body weight and those with underlying renal impairment (see section "Pharmacokinetics"). This could result in a higher risk of developing EGFR mediated

adverse events such as diarrhoea, rash/acne and stomatitis. Closer monitoring is recommended in patients with these risk factors.

Interstitial Lung Disease (ILD)
There have been reports of ILD or ILD-like events (such as Lung infiltration, Pneumonitis, Acute respiratory distress syndrome, Alveolitis allergic), including fatalities, in patients receiving GIOTRIF for treatment of NSCLC. Drug related ILD-like events were reported in 0.7% of patients treated with GIOTRIF across all clinical trials (including 0.5% of patients with CTCAE Grade ≥ 3 ILD-like adverse reactions (see Side Effects). Patients with a history of ILD have not been studied. Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnoea, cough, fever) should be performed to exclude ILD. GIOTRIF should be interrupted pending investigation of these symptoms. If ILD is diagnosed, GIOTRIF should be permanently discontinued and appropriate treatment instituted as necessary (see "Dosage and administration").

Severe hepatic impairment
Hepatic failure, including fatalities, has been reported during treatment with GIOTRIF in less than 1% of patients. In these patients, confounding factors have included pre-existing liver disease and/or comorbidities associated with progression of underlying malignancy. Periodic liver function testing is recommended in patients with pre-existing liver disease. GIOTRIF dose interruption may become necessary in patients who experience worsening of liver function (see section "Dosage and administration"). In patients who develop severe hepatic impairment while taking GIOTRIF, treatment should be discontinued.

Gastrointestinal perforations
Gastrointestinal perforation, including fatalities, has been reported during treatment with GIOTRIF in 0.2% of patients across all randomized controlled clinical trials. In the majority of cases, gastrointestinal perforation was associated with other known risk factors, including concomitant medications such as corticosteroids, NSAIDs, or anti-angiogenic agents, an underlying history of gastrointestinal ulceration, underlying diverticular disease, age, or bowel metastases at sites of perforation. In patients who develop gastrointestinal perforation while taking GIOTRIF, treatment should be permanently discontinued.

Keratitis
Symptoms such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye should be referred promptly to an ophthalmology specialist. If a diagnosis of ulcerative keratitis is confirmed, treatment with GIOTRIF should be interrupted or discontinued. If keratitis is diagnosed, the benefits and risks of continuing treatment should be carefully considered. GIOTRIF should be used with caution in patients with a history of keratitis, ulcerative keratitis or severe dry eye. Contact lens use is also a risk factor for keratitis and ulceration (see section Adverse Reactions).

Left ventricular function
Left ventricular dysfunction has been associated with HER2 inhibition. Based on the available clinical trial data, there is no suggestion that GIOTRIF causes an adverse effect on cardiac contractility. However, GIOTRIF has not been studied in patients with abnormal left ventricular ejection fraction (LVEF) or those with significant cardiac history.

In patients with cardiac risk factors and those with conditions that can affect LVEF, cardiac monitoring, including an assessment of LVEF at baseline and during GIOTRIF treatment, should be considered. In patients who develop relevant cardiac signs/symptoms during treatment, cardiac monitoring including LVEF assessment should be considered.
In patients with an ejection fraction below the institution's lower limit of normal, cardiac consultation as well as GIOTRIF treatment interruption or discontinuation should be considered.

P-glycoprotein (P-gp) interactions
Strong inhibitors of P-gp if administered prior to GIOTRIF may lead to increased exposure to afatinib and therefore should be used with caution. If P-gp inhibitors need to be taken, they should be administered simultaneously with or after GIOTRIF. Concomitant treatment with strong inducers of P-gp may decrease exposure to afatinib (see sections "Dosage and administration", "Interactions", and "Pharmacokinetics").

Lactose
GIOTRIF contains lactose. Patients with rare hereditary conditions of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Interactions

P-glycoprotein (P-gp) interactions
Based on *in vitro* data, afatinib is a substrate of P-gp. Based on clinical data, concomitant administration of strong P-gp inhibitors or inducers may alter exposure to afatinib. Results of a drug interaction trial demonstrated that GIOTRIF can be safely combined with P-gp inhibitors (such as ritonavir) as long as the inhibitor is administered simultaneously with or after GIOTRIF. If administered prior to GIOTRIF, strong P-gp inhibitors (including but not limited to ritonavir, cyclosporine A, ketoconazole, itraconazole, erythromycin, verapamil, quinidine, tacrolimus, nelfinavir, saquinavir, and amiodarone) may increase exposure to afatinib and should be used with caution (see section "Dosage and Administration", "Special Warnings and Precautions" and "Pharmacokinetics").

Strong P-gp inducers (including but not limited to rifampicin, carbamazepine, phenytoin, phenobarbital or St. John's Wort) may decrease exposure to afatinib (see section "Special Warnings and Precautions" and "Pharmacokinetics").

Food effect on afatinib
Co-administration of a high-fat meal with GIOTRIF resulted in a significant decrease of exposure to afatinib by about 50% in regard to C_{max} and 39% in regard to $AUC_{0-\infty}$. GIOTRIF should be administered without food (see sections "Dosage and Administration" and "Pharmacokinetics").

Fertility, pregnancy and lactation

Pregnancy

Nonclinical studies with afatinib have shown no signs of teratogenicity up to and including maternally lethal dose levels. Adverse changes were restricted to overtly toxic dose levels (see section "Toxicology").
There are no studies in pregnant women using GIOTRIF. The potential risk for humans is thus unknown. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with GIOTRIF. Adequate contraceptive methods should be used during therapy and for at least 2 weeks after the last dose. If GIOTRIF is used during pregnancy or if the patient becomes pregnant while receiving GIOTRIF, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding
Based on nonclinical data (see section "Toxicology"), it is likely that afatinib is excreted in human milk. A risk to the nursing child cannot be excluded. Mothers should be advised against breast-feeding while receiving GIOTRIF.

Fertility
Fertility studies in humans have not been performed with GIOTRIF. Available nonclinical toxicology data have shown effects on reproductive organs at higher doses (see section "Toxicology"). Therefore, an adverse effect of GIOTRIF therapy on human fertility cannot be excluded.

Effects on ability to drive and use machines

No studies on the effects on the ability to drive or operate machinery have been performed.

Adverse Reactions

Adverse Drug Reaction Overview
The safety evaluation of GIOTRIF is based on the data from more than 3865 patients, including 2135 NSCLC patients treated with GIOTRIF monotherapy at or above the recommended dose. The types of adverse drug reactions (ADRs) were generally associated with the EGFR inhibitory mode of action of afatinib. The most frequent ADRs were diarrhea and skin related adverse events as well as stomatitis and paronychia. ILD-like adverse reactions were reported in 0.7% in all GIOTRIF treated patients and 1.3% of patients treated with GIOTRIF in the pivotal clinical trial. Overall, dose reduction led to a lower frequency of common adverse reactions. In patients treated with once daily GIOTRIF 40 mg dose reductions due to ADRs occurred in 57% of the patients. Discontinuation due to ADRs diarrhea and rash was 1.3% and 0% respectively. Bullous, blistering and exfoliative skin conditions have been reported including rare case suggestive of Steven-Johnson.

Tabulated list of adverse reactions

Table 2 summarises the frequencies of ADRs from all NSCLC trials and from post-marketing experience with daily GIOTRIF doses of 40 mg as monotherapy. The following terms are used to rank the ADRs by frequency: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Summary of ADRs per frequency category

Body System	Very common	Common	Uncommon	Rare
Infections and infestations	Paronychia[1]	Cystitis		
Metabolism and nutrition disorders	Decreased appetite	Dehydration Hypokalaemia		
Nervous system disorders		Dysgeusia		
Eye disorders		Conjunctivitis Dry eye	Keratitis	
Respiratory, thoracic and mediastinal disorders	Epistaxis	Rhinorrhoea	Interstitial lung disease	
Gastrointestinal disorders	Diarrhoea Stomatitis[2] Nausea Vomiting	Dyspepsia Cheilitis	Pancreatitis Gastrointestinal perforation	
Hepatobiliary disorders		Alanine aminotransferase increased Aspartate aminotransferase increased		
Skin and subcutaneous tissue disorders	Rash[3] Dermatitis acneiform[4] Pruritus[5] Dry skin[6]	Palmar-plantar erythrodysaesthesia syndrome Nail disorders[8]		Stevens-Johnson syndrome[7] Toxic epidermal necrolysis[7]
Musculoskeletal and connective tissue disorders		Muscle spasms		
Renal and urinary disorders		Renal impairment/ Renal failure		
General disorders and administration site conditions		Pyrexia		
Investigations		Weight decreased		

[1] Includes Paronychia, Nail infection, Nail bed infection
[2] Includes Stomatitis, Aphthous stomatitis, Mucosal inflammation, Mouth ulceration, Oral mucosa erosion, Mucosal erosion, Mucosal ulceration
[3] Includes group of rash preferred terms

[4] Includes Acne, Acne pustular, Dermatitis acneiform
[5] Includes Pruritus, Pruritus generalised
[6] Includes Dry skin, Skin chapped
[7] Based on post-marketing experience
[8] Includes Nail disorder, Onycholysis, Nail toxicity, Onychoclasis, Ingrowing nail, Nail pitting, Onychomadesis, Nail discoloration, Nail dystrophy, Nail ridging, and Onychogryphosis

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Pivotal phase III trial (LUX-Lung 3)

In the pivotal LUX-Lung 3 study, a total of 229 patients not previously treated with an EGFR inhibitor (EGFR TKI-naïve patients) were treated with GIOTRIF with a starting dose of 40 mg once daily until disease progression or intolerance. In the control arm, a total of 111 patients received pemetrexed/cisplatin up to 6 cycles. The median duration of treatment were 336 and 105 days in the GIOTRIF and chemotherapy arms, respectively. Adverse event reported in ≥ 10% of GIOTRIF-treated patients are presented in Table 3 below. The incidence of diarrhea and rash AEs was higher in the GIOTRIF treated patients than in those treated with pemetrexed/cisplatin.
Overall, serious AEs were reported in 28.8% patients. The most frequent serious AEs (≥1%) were diarrhea (6.6%), vomiting (4.8%), dyspnea (1.7%), fatigue (1.7%), dehydration (1.3%), pneumonia (1.3%), and stomatitis (1.3%). Fatal adverse events related to GIOTRIF included one event each of dyspnea, ARDS (ILD), sepsis and death (not otherwise specified).
Clinical trial of GIOTRIF excluded patients with an abnormal left ventricular ejection fraction (LVEF), i.e., below the institutional lower limit of normal. In LUX-Lung 3, all patients were evaluated for LVEF at screening and every 9 weeks thereafter in the GIOTRIF-treated group and as needed in the pemetrexed/cisplatin group. More GIOTRIF-treated patients (2.2%; n=5) experienced ventricular dysfunction (defined as diastolic dysfunction, left ventricular dysfunction, or ventricular dilation; all < Grade 3) compared to the chemotherapy-treated patients (0.9%; n=1).
From pooled data of 2135 NSCLC patients treated with GIOTRIF monotherapy, events of cardiac failure (acute left ventricular failure, cardiac failure, and diastolic dysfunction) assessed as drug related by the investigator have been reported uncommonly (<1%).
Dose reduction due to adverse events occurred in 57% of GIOTRIF-treated patients. Overall dose reduction appeared to have led to a lower frequency of common adverse events (e.g. after first dose reduction, frequency for diarrhea regardless of causality decreased from 96% to 52%).
The most common (>1%) AEs leading to dose reduction in patients treated with GIOTRIF included diarrhea (19.7%), rash (19.2%), paronychia (13.1%), stomatitis (10%), decreased appetite (3.1%), vomiting (3.1%), Palmar-plantar erythrodysesthesia syndrome (1.7%), ALT increase (1.3%), AST increase (1.3%), glomerular filtration rate (GFR) decreased (1.3%), nausea (1.3%), and pruritus (1.3%).
Discontinuation of GIOTRIF therapy due to AEs occurred in 14% of patients.
Discontinuation of GIOTRIF therapy due to ADRs occurred in 8% patients. The most common (≥0.5%) AEs that led to discontinuation in the pivotal study were diarrhea (1.3%), dyspnea (0.9%), ILD (0.9%), pleural effusion (0.9%), pneumonia (0.9%) and paronychia (0.9%).

Table 3 : Adverse Events Reported in ≥10% of GIOTRIF-Treated Patients in LUX-Lung 3.

	GIOTRIF n=229			Pemetrexate/Cisplatin n=111		
Adverse Events[a]	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All Grades (%)	Grade 3 (%)	Grade 4 (%)
Gastrointestinal disorders						
Diarrhea	96	15	0	23	2	0
Stomatitis[1]	71	8	<1	15	1	0
Nausea	25	1	0	68	4	0
Vomiting	23	4	0	47	3	0
Constipation	13	0	0	35	0	0
Cholitis	12	0	0	1	0	0
Skin and Subcutaneous tissue disorders						
Rash[2]	71	14	0	11	0	0
Dermatitis acneiform[3]	35	3	0	0	0	0
Pruritus[4]	21	0	0	1	0	0
Dry skin[5]	31	0	0	2	0	0
Alopecia	13	0	0	18	0	0
Nail Disorder						
Steven's Johnson Syndrome*						
Toxic Epidermal Necrolysis*						
Infections and Infestations						
Paronychia[6]	58	11	0	0	0	0
Nasopharyngitis	14	0	0	8	0	0
Cystitis[7]	13	1	0	5	0	0
Upper respiratory tract infection	11	0	0	4	0	0
Metabolism and Nutrition Disorders						
Decreased appetite	29	4	0	55	4	0
Hypokalemia[8]	11	2	2	5	3	1
Respiratory, thoracic and mediastinal disorders						
Epistaxis	17	0	0	2	1	0
Cough	15	0	0	19	1	0
Rhinorrhea[9]	11	0	0	6	0	0
Investigations						
Weight decreased						
Alanine	17	1	0	14	1	0
aminotransferase increased	11	2	0	4	0	0
Psychiatric disorder						
Insomnia	15	0	0	9	0	0
Nervous system disorders						
Headache	14	0	0	17	0	0
Dizziness	11	0	0	11	0	0
General disorders and administration site conditions						
Pyrexia[10]	12	0	0	6	0	0
Musculoskeletal and connective tissue disorder						
Back pain	14	0	0	12	2	0

Eye disorders Conjunctivitis[11]	11	0	0	3	0	0

[a] Grades are based on NCI CTCAE v 3.0
[1] Includes stomatitis, apthous stomatitis, mucosal inflammation, mouth ulceration, oral mucosa erosion, mucosal erosion, mucosal ulceration
[2] Includes group of rash preferred terms
[3] Includes acne, acne pustular, dermatitis acneiform
[4] Includes pruritus, pruritus generalized
[5] Includes dry skin, skin chapped
[6] Includes paronychia, nail infection, nail bed infection
[7] Includes cystitis, urinary tract infection
[8] Includes hypokalemia, blood potassium decreased
[9] Includes rhinorrhea, nasal inflammation
[10] Includes pyrexia, body temperature increased
[11] Includes conjunctivitis, conjunctival irritation, conjunctival hyperemia
• derived from post-marketing experience

Table 4 : Adverse Reactions of Laboratory Abnormalities from Investigations SOC Reported in ≥ 10% of GIOTRIF -Treated Patients in LUX-lung 3

	GIOTRIF n=229		Pemetrexate/Cisplatin n=111	
Adverse reaction	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Alanine aminotransferase increased	11	2	4	0
Hypokalaemia[1]	11	4	5	4

[1] Includes hypokalemia, blood potassium decreased
SOC = System Organ Class

Adverse Events Considered Drug Related to GIOTRIF by the Investigator in 1 to 10% patients in LUX-Lung 3 (All Grades)

Infection and Infestations : Cystitis (4%), Rhinitis (2%), Cellulitis (1%), Herpes zoster (1%), Upper respiratory tract infection (1%)
Blood and lymphatic system disorders : Anemia (3%), Leukopenia (2%)
Gastrointestinal disorders : Dyspepsia (4%), Dry Mouth (4%), Abdominal pain (3%), Constipation (3%), Abdominal distension (2%), Abdominal pain upper (2%), Gastritis (2%), Gastroesphageal reflux disease (2%), Dysphagia (1%), Abdominal discomfort (1%), Gingival bleeding (1%), Proctalgia (1%), Tongue ulceration (1%)
Hepatobiliary disorders : Hepatic functions abnormal (2%)
Nervous system disorder: Dysgeusia (7%), Headache (5%), Dizziness (4%), Hypoesthesia (2%)
Musculoskeletal and connective tissue disorders: Muscle spasm (3%), Back pain (2%), Myalgia (2%), Arthralgia (1%), Musculoskeletal chest pain (1%)
Skin and subcutaneous tissue disorders: Alopecia (10%), Palmar-plantar erythrodysesthesia syndrome (7%), Nail disorder (5%), Hypertrichosis (3%), Pain of skin (3%), Skin hyperpigmentation (1%)
Renal and urinary disorders: Renal impairment/Renal failure (4%), Proteinuria (1%)
Eye disorders: Conjunctivitis (8%), Dry eye (5%), Keratitis (2%), Blepharitis (2%), Lacrimation increased (2%), Cataract (1%), Eye discharge (1%), Vision blurred (1%)
Investigations: Alanine aminotransferase increased (7%), Aspartate aminotransferase increased (5%), Blood alkaline phosphatase increased (2%), Hemoglobin decreased (1%)
General disorders and administration site conditions: Pyrexia (5%), Asthenia (4%), Edema peripheral (3%), Edema (2%), Xerosis (2%), Chest pain (1%)
Psychiatric disorders: Insomnia (5%)

Metabolism and nutritions disorders: Hypokalemia (6%), Dehydration (2%)
Respiratory, thoratic and mediastinal disorders: Rhinorrhea (10%), Cough (3%), Nasal dryness (3%), Dyspnea (2%), Oropharyngeal pain (2%), Hemoptysis (1%), Interstitial lung disease (1%)
Vascular disorders: Hypertension (2%)
Injury, poisoning and procedural complications : Wound (1%)

Clinically important, afatinib-related AEs < 1% include:
Blood and lymphatic system disorders: Lymphopenia, Neutropenia
Cardiac disorders: Mitral valve incompetence
Gastrointestinal disorders: Pancreatitis acute
General disorders and administration site conditions: Death
Infections and infestations: sepsis
Investigations: Blood amylase increased, Blood creatine phosphokinase increased, Neutrophil count decreased
Metabolism and nutrition disorders: Hypocalcaemia, Hyponatraemia
Respiratory, thoracic and mediastinal disorders: Pulmonary embolism
Skin and subcutaneous tissue disorders: Hyperkeratosis

In the LUX-Lung 6 (1200.34) trial a total of 239 EGFR TKI naïve patients were treated with GIOTRIF with a starting dose of 40 mg once daily. A total of 113 patients were treated with gemcitabine/cisplatin. The overall incidence of ADRs in patients treated with GIOTRIF was similar to gemcitabine/cisplatin (98.7% vs. 99.1%). The incidences of diarrhoea (88.7% vs. 10.6%) and rash/acne (81.2% vs. 8.8%) ADRs were higher in the GIOTRIF-treated patients than in patients treated with gemcitabine/cisplatin. Dose reductions due to adverse events occurred in 33.1% of GIOTRIF-treated patients and in 26.5% of gemcitabine/cisplatin-treated patients.
Discontinuations of study medication due to ADRs were less frequent in patients who received GIOTRIF compared with gemcitabine/cisplatin (6.3% vs. 39.8%). In patients treated with GIOTRIF, the incidences of discontinuations due to the ADRs diarrhoea and rash/acne were 0% and 2.5%, respectively.

In the pivotal LUX-Lung 8 (1200.125) trial a total of 392 patients with Squamous NSCLC were treated with GIOTRIF with a starting dose of 40 mg once daily and a total of 395 patients were treated with 150 mg erlotinib once daily. All patients were required to have 1) been previously treated with at least 4 cycles of platinum based chemotherapy, 2) recovered from previous therapy related toxicities, 3) an ECOG status of 0 or 1, and 4) adequate organ function including a normal left ventricular ejection fraction (LVEF). Patients continued treatment until progression of disease or intolerance to treatment. The mean duration of treatment was no longer in the afatinib treatment group (120.8 days) than in the erlotinib treatment group (97.2 days).

Adverse events reported in ≥ 10% of GIOTRIF®-treated patients are presented in the Table 5 below. The incidence of diarrhea, stomatitis, and paronychia were substantially higher in the GIOTRIF-treated patients compared to erlotinib.
Overall, serious AEs were reported in 44.1% of patients in both treatment groups. The most frequent AEs for GIOTRIF were pneumonia (6.6%), malignant neoplasm progression (5.9%), diarrhea (4.6%), dehydration (3.1%) and dyspnea (3.1%). Events of dehydration were generally associated with diarrhea. Adverse events with a fatal outcome were reported in 19.6 % of patients in the GIOTRIF group and 18.0% in the erlotinib group. Fatal events were mainly related to disease progression (e.g., malignant

neoplasm progression) and/or signs and symptoms thereof (e.g., dyspnea). Fatal AEs were classified as drug-related for 6 patients (1.5%) in the GIOTRIF group and 5 patients (1.3%) in the erlotinib group. In the GIOTRIF treatment group, 2 drug-related deaths were designated within the preferred term (PT) interstitial lung disease and 1 death was attributed to each of the following PTs; pneumonia, respiratory failure, acute renal failure, and general physical health deterioration. In the erlotinib treatment group, the 5 drug-related deaths were attributed to peritonitis, ILD, pneumonia, pneumotitis and intestinal obstruction.

The most frequently reported AEs in the erlotinib group were dyspnea (7.6%), pneumonia (4.1%), malignant neoplasm progression (4.1%), and respiratory failure (3.0%).

Overall, 26.5% in the GIOTRIF treatment group had AEs that led to a dose reduction. The most frequent of these events were diarrhea (14.8%), rash/acne (5.9%), and stomatitis (3.1%). In the erlotinib treatment group, 14.2% had AEs that led to a dose reduction. The most frequent AEs were rash/acne+ (9.4%), and diarrhea (3.5%).

AEs that led to treatment discontinuation were reported for 20.2% of patients in the GIOTRIF group. The AEs that most frequently led to treatment discontinuation were diarrhea (4.1%) and rash/acne (2.6%). Drug-related AEs led to discontinuation for 10.5% of patients.
In the erlotinib group, AEs that led to treatment discontinuation were reported for 17.0% of patients. The AEs that most frequently led to treatment discontinuation were diarrhea (1.5%) and rash/acne (2.0%). Drug-related AEs led to discontinuation for 4.8% of patients.

Table 5: Adverse Events Reported in ≥ 10% of GIOTRIF®-Treated Patients in LUX-Lung 8

	Afatinib N=392			Erlotinib N=395		
Adverse Events	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Total with adverse events	100	32	6	98	35	5
Gastrointestinal disorders						
Diarrhea	75	10	0.8	41	3	0.3
Stomatitis	30	4		11	0.5	
Nausea	21	2		16	1	0.3
Vomiting	13	0.8		10	1	0.3
Constipation	11			11	0.3	
Skin and subcutaneous tissue disorders						
Rash/acne	70	7		70	11	
Rash	61	5		57	8	
Acne	14	1		18	3	
Pruritus	10	0.3		13		
Dry Skin	9	0.5		12		

General disorders and administrative site conditions Fatigue	34	5	0.3	30	6	0.8
Metabolism and nutrition disorders Decreased appetite	25	3		26	2	
Respiratory, thoracic and mediastinal disorders Dyspnea Cough Hemoptysis	20 17 13	3 0.5 0.5	0.8	24 18 12	5 0.5 0.5	1.0 0.3
Infections and infestations Paronychia	11	0.5		5	0.3	
Investigations Weight decreased	10	0.5		13	0.5	
Blood and lymphatic system disorders Anemia	9	2	0.5	11	2	

Table 6: Laboratory Abnormalities Occurring in ≥ 10% GIOTRIF Arm and at ≥ 2% Higher Incidence than in Erlotinib Arm in LUX-Lung 8

Laboratory Abnormality	GIOTRIF® N=392		Erlotinib N=395	
	All Grades (%)	Grades 3-4 (%)	All Grades (%)	Grades 3-4 (%)
Increased alkaline phosphate	34	2	31	0
Decreased white blood cell count	12	1	8	1
Decreased potassium	11	1	8	1

Adverse Events Considered Drug Related to GIOTRIF by the Investigator in 1 to 10% of Patients in LUX-Lung 8 (All Grades)

Blood and lymphatic system disorders: Anemia (3%)
Eye disorders: Conjunctivitis (2%), Dry eye (2%)
Gastrointestinal disorders: Vomitting (8%), Mouth ulceration (4%), Abdominal pain upper (2%), Abdominal pain (2%), Oral pain (2%), Constipation (2%), Dyspepsia (1%), Dry mouth (1%)
General disorders and administration site conditions: Fatigue (8%), Asthenia (6%)
Infections and Infestations: Folliculitis (2%), Fungal infection (1%), Rhinitis (1%)

Investigations: weight decreased (3%), Alanine aminotransferase increased (1%), Blood creatinine increased (1%), Blood magnesium decreased (1%)
Metabolism and nutrition disorders: Dehydration (4%), Hypokalemia (2%)
Musculoskeletal and connective tissue disorders: Muscle spasm (1%)
Nervous system disorders: Dysgeusia (2%)
Renal and urinary disorders: Renal failure acute (1%)
Respiratory, thoracic and mediastinal disorders: Epistaxis (2%), Dyspnea (2%), Cough (1%), Rhinorrhea (1%)
Skin and subcutaneous tissue disorders: Dermatitis acneiform (10%), Dry skin (9%), Pruritis (8%), Acne (4%), Skin exfoliation (3%), Skin fissures (3%), Skin toxicity (2%), Dermatitis (2%), Plamar-plantar erythrodysesthesia (2%), Alopecia (1%), Erythema (1%), Xeroderma (1%).

Overdose

Symptoms
The highest dose of GIOTRIF studied in a limited number of patients in Phase I clinical trials was 160 mg once daily for 3 days and 100 mg once daily for 2 weeks. The adverse reactions observed at this dose were primarily dermatological (rash/acne) and gastrointestinal events (especially diarrhoea). Overdose in 2 healthy adolescents involving the ingestion of 360 mg each of GIOTRIF (as part of a mixed drug ingestion) was associated with adverse drug reactions of nausea, vomiting, asthenia, dizziness, headache, abdominal pain and elevated amylase (< 1.5 times ULN). Both subjects recovered from these adverse events.

Treatment
There is no specific antidote for overdose with GIOTRIF**.** In cases of suspected overdose, GIOTRIF should be withheld and supportive care instituted.
If indicated, elimination of unabsorbed afatinib may be achieved by emesis or gastric lavage.

Pharmacological properties

Pharmacotherapeutic group: other antineoplastic agents – protein kinase inhibitors, ATC code: L01XE13.

Mechanism of action
Afatinib is a potent and selective, irreversible ErbB Family Blocker. Afatinib covalently binds to and irreversibly blocks signalling from all homo- and heterodimers formed by the ErbB family members EGFR (ErbB1), HER2 (ErbB2), ErbB3 and ErbB4.

Pharmacodynamic effects
Aberrant ErbB signalling triggered by, for instance, EGFR mutations and/or amplification, HER2 amplification or mutation and/or ErbB ligand or receptor overexpression contributes to the malignant phenotype in subsets of patients across multiple cancer types.
In non-clinical disease models with ErbB pathway deregulation, afatinib as a single agent effectively blocks ErbB receptor signalling resulting in tumour growth inhibition or tumour regression. Anti-tumour activity of afatinib was demonstrated in HER2

overexpressing models. Various ErbB pathway aberrations (e.g. EGFR overexpression or mutation) were also the most likely underlying cause for the activity of afatinib in Lung Cancer models. NSCLC models with either L858R or Del 19 EGFR mutations are particularly sensitive to afatinib treatment. In NSCLC, the acquisition of a secondary T790M mutation is a major mechanism of acquired resistance to afatinib and gene dosage of the T790M-containing allele correlates with the degree of resistance in vitro. The T790M mutation is found in approximately 50% of patients' tumours upon disease progression on afatinib, for which T790M targeted EGFR TKIs may be considered as a next line treatment option.

The efficacy and safety of GIOTRIF as second line treatment of patients with NSCLC of squamous histology was investigated in an open-label active controlled trial LUX-Lung 8.

Clinical trials

GIOTRIF *in EGFR mutation positive patients naïve to EGFR TKI treatment*

LUX-Lung 3 (1200.32)

In the first-line setting, the efficacy and safety of GIOTRIF in patients with EGFR mutation-positive locally advanced or metastatic NSCLC (stage IIIB or IV) were assessed in a global, randomised, multicentre, open-label trial (LUX-Lung 3). Patients naïve to prior systemic treatment for their advanced or metastatic disease were screened for the presence of 29 different EGFR mutations using a polymerase chain reaction (PCR) based method (TheraScreen®: EGFR29 Mutation Kit, Qiagen Manchester Ltd). Patients (N=345) were randomised (2:1) to receive GIOTRIF 40 mg orally once daily (N=230) or up to 6 cycles pemetrexed/cisplatin (N=115). Randomisation was stratified according to EGFR mutation status (L858R; Del 19; other) and race (Asian; non-Asian). Mean duration of treatment was 336 and 105 days for the GIOTRIF and chemotherapy arms, respectively.

The primary endpoint of PFS (independent review, 221 events) showed a statistically significant improvement in the median PFS for patients treated with GIOTRIF compared with patients treated with chemotherapy (media PFS 11.1 vs. 6.9 months). When comparing the pre-specified subgroup of common (L858R or Del 19) EGFR mutations, the difference in PFS was further pronounced (median PFS 13.6 vs. 6.9 months). The percentages of patients being alive and progression-free (PFS rate) at 12 months were 46.5% in patients treated with GIOTRIF and 22% in patients treated with chemotherapy for the overall trial population, and 51.1% vs. 21.4% in the subgroup of common mutations.

The subgroup of "other" (uncommon) mutations was small (N=37; 11%) and genetically heterogeneous (10 different molecular subtypes with unequal distribution between the treatment groups) thereby limiting the value and interpretation of the pooled statistical analyses in this subset. Individual responses and prolonged disease stabilisation were observed in some patients with uncommon mutations.

The Kaplan-Meier curves of the primary PFS analysis are shown in Figure 1 and efficacy results are summarised in Table 7. At the time of primary PFS analysis a total of 45 (20%) patients treated with GIOTRIF and 3 (3%) patients treated with chemotherapy were known to be alive and progression-free and thus censored in Figure 1.

Figure 1: Kaplan-Meier Curve for PFS by independent review by treatment group in LUX-Lung 3 Trial (Overall Population):

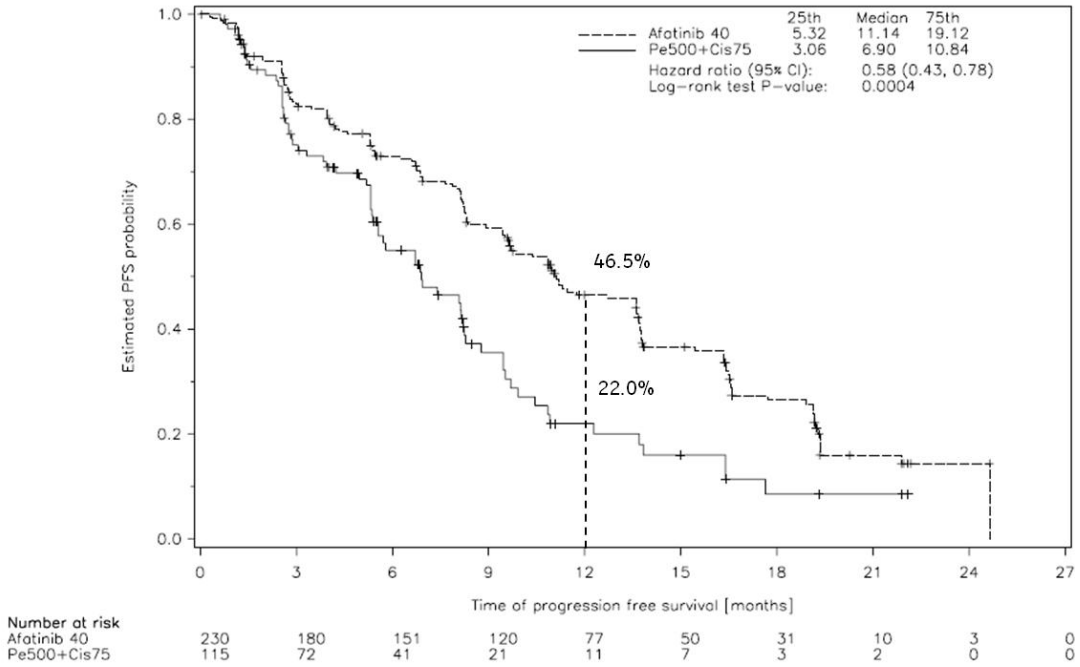


Table 7: Efficacy results of GIOTRIF vs. pemetrexed/cisplatin (LUX-Lung 3 Trial) based on the primary PFS analysis as of 9 February 2012 (Independent review)

	GIOTRIF (N=230)	**Pemetrexed/ Cisplatin** (N=115)	**Hazard Ratio/ Odds Ratio (95%CI) p-value[4]**
PFS, Overall Trial Population			
Months (median)	**11.1**	**6.9**	HR 0.58 (0.43-0.78)
1-year PFS Rate	46.5%	22%	0.0004
18-months PFS Rate	26.4%	8.6%	
PFS, Patients with L858R or Del 19 Mutations[1]			
Months (median)	**13.6**	**6.9**	HR 0.47 (0.34-0.65)
1-year PFS Rate	51.1%	21.4%	< 0.0001
18-months PFS Rate	28.6%	7.4%	
Objective Response Rate (CR+PR)[2]	**56.1%**	**22.6%**	OR 4.66 (2.77-7.83) < 0.0001
Disease Control Rate (CR+PR+SD)[2]	**90.0%**	**80.9%**	OR 2.14 (1.13-4.04) 0.0189

Response Duration Months (median)	**11.1**	**5.5**	-
Overall Survival (OS), Overall Trial Population **Months (median)** [3]	**28.2**	**28.2**	HR 0.88 (0.66, 1.17) 0.39

[1] N=308 (GIOTRIF: 204, pemetrexed/cisplatin: 104)
[2] CR=complete response; PR=partial response; SD=stable disease
[3] OS analysis as of December 2013
[4] p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate based on logistic regression

The PFS benefit of GIOTRIF was accompanied by improvement in disease-related symptoms, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30 and QLQ-LC13). GIOTRIF significantly delayed the time to deterioration for the pre-specified symptoms of cough (HR 0.60; p=0.0072) and dyspnoea (HR 0.68; p=0.0145) by more than 7 months when compared with chemotherapy. Time to deterioration of pain was also longer with GIOTRIF but did not reach statistical significance (HR 0.83; p=0.1913). Significantly more patients treated with GIOTRIF compared with those treated with chemotherapy had improvement for dyspnoea (64% vs. 50%; p=0.0103). A trend favouring GIOTRIF was observed for pain (59% vs. 48%; p=0.0513), with individual items of pain reaching significance ('Have pain': 56.0% vs. 40.0%; p=0.0095; 'Pain in chest': 51.0% vs. 37.0%; p=0.0184; 'Pain in arm or shoulder': 41.0% vs. 26.0%; p=0.0103). For cough, numerically more patients improved on GIOTRIF (67% vs. 60%; p=0.2444).
Mean scores over time for health-related quality of life (HRQoL) were measured using the EORTC QLQ-C30. Mean scores over time for overall quality of life and global health status were significantly better for GIOTRIF compared with chemotherapy. Mean scores were significantly better in 3 of the 5 functioning domains (physical, role, cognitive) and showed no difference in the emotional and social functioning domains.

LUX-Lung 6 (1200.34)

The efficacy and safety of GIOTRIF in Asian patients with EGFR mutation-positive locally advanced or metastatic adenocarcinoma of the lung (stage IIIB/IV) was assessed in a randomised, multicenter, open-label trial (LUX-Lung 6). Similar to LUX-Lung 3, patients naïve to prior systemic treatment for their advanced or metastatic disease were screened for the presence of 29 different EGFR mutations using a PCR based method (TheraScreen®: EGFR29 Mutation Kit, Qiagen Manchester Ltd). Patients (N=364) were randomised (2:1) to receive GIOTRIF 40 mg orally once daily (N=242) or up to 6 cycles gemcitabine/cisplatin (N=122). Randomisation was stratified according to EGFR mutation status (L858R; Del 19; other). Dose escalation of GIOTRIF to 50 mg was allowed after the first treatment cycle (21 days) if patients had no or limited drug-related adverse events (i.e. absence of diarrhoea, skin rash, stomatitis, and/or other drug related events above CTCAE Grade 1), were compliant, and had no prior dose reduction. Among randomized patients, 65% were female; the median age was 58 years and all patients were Asian. Patients with common (L858R or Del 19) EGFR mutations accounted for 89% of the study population.
The primary endpoint of PFS (central independent review, 221 events) showed a statistically significant improvement in PFS for patients treated with GIOTRIF compared

with patients treated with chemotherapy (median PFS: 11.0 vs. 5.6 months). When comparing the prespecified subgroup of common (L858R or Del 19) EGFR mutations, the difference in median PFS remained constant (11.0 vs. 5.6 months). The percentages of patients being alive and progression-free (PFS rate) at 12 months were 46.7% in patients treated with GIOTRIF® and 2.1% in patients treated with chemotherapy for the overall trial population, and 56.4% vs. 4.4% in the subgroup of common mutations.
The Kaplan-Meier curves of the primary PFS analysis are shown in Figure 2, and efficacy results are summarised in Table 8. At the time of primary PFS analysis, a total of 57 (15.7%) patients treated with GIOTRIF were known to be alive and progression-free and thus censored in Figure 2.

Figure 2 Kaplan-Meier curves for PFS by independent review by treatment group in LUX-Lung 6 Trial (Primary Analysis, Overall Population)

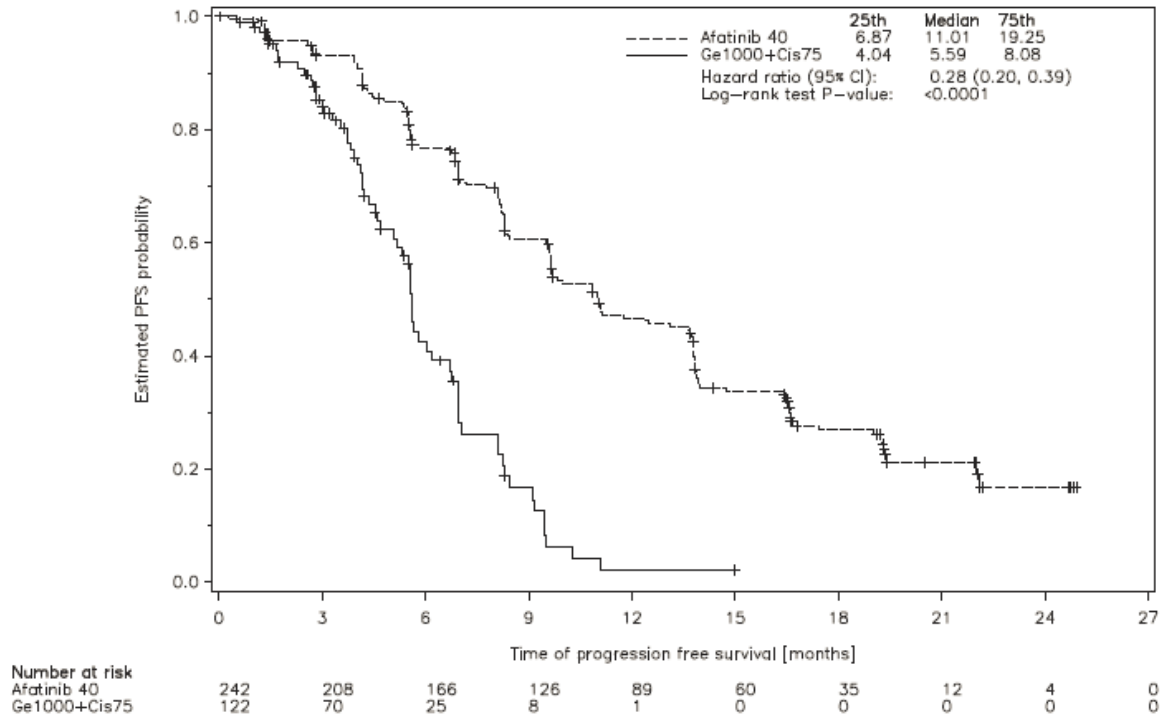


Table 8 : Efficacy results for GIOTRIF® vs. gemcitabine/cisplatin (LUX-Lung 6 Trial) based on the primary PFS analysis as of 29 October 2012 (Independent review)

	GIOTRIF (N=242)	Gemcitabine/ Cisplatin (N=122)	Hazard Ratio/ Odds Ratio (95%CI) p-value[4]

PFS, Overall Trial Population Months (median) 1-year PFS Rate 18-months PFS Rate	 11.0 46.7% 26.8%	 5.6 2.1% 0.0%	 HR 0.28 (0.20-0.39) <0.0001
PFS, Patients with L858R or Del 19 Mutations[1] Months (median) 1-year PFS Rate 18-months PFS Rate	 11.0 56.4% 26.8%	 5.6 4.4% 0.0%	 HR 0.25 (0.18-0.35) < 0.0001
Objective Response Rate (CR+PR)[2]	66.9%	23.0%	OR 7.28 (4.36-12.18) < 0.0001
Disease Control Rate (CR+PR+SD)[2]	92.6%	76.2%	OR 3.84 (2.04-7.24) <0.0001
Response Duration Months (median)	9.7	4.3	
Overall Survival (OS), Overall Trial Population Months (median)[3]	23.1	23.5	HR 0.93 (0.72, 1.22) 0.6137

1 N=324 (GIOTRIF®: 216, gemcitabine/cisplatin: 108)
2 CR=complete response; PR=partial response; SD=stable disease
3 Main OS analysis as of 27 December 2013 (when 246 patients had died)
4 p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate and Disease Control Rate based on logistic regression

The analysis of PFS based on investigator review yielded similar results (HR=0.26, CI= 95% 0.19 – 0.36; p<0.0001; median PFS: 13.7 vs. 5.6 months) as the analysis based on the independent review. The effect on PFS was consistent across major subgroups, including gender, age, race, ECOG status, and mutation type (L858R, Del 19) in both the independent and investigator reviews. Based on investigator review, ORR was 74.4% vs. 31.1% and DCR was 93.0% vs. 75.4% in GIOTRIF-treated patients compared with chemotherapy-treated patients. In the pre-defined subgroup of common EGFR mutations (Del 19, L858R) for GIOTRIF (N=216) and chemotherapy (N=108) the median OS was 23.6 months vs. 23.5 months (HR=0.83, 95% CI (0.62-1.09), p=0.1756). In the pre-defined EGFR mutation subgroups, the median OS with first-line GIOTRIF vs chemotherapy was 31.4 months vs 18.4 months (HR=0.64, (95% CI 0.44-0.94), p=0.0229) in patients with Del 19 (n=186) and 19.6 months vs 24.3 months (HR=1.22, (95% CI: 0.81-1.83), p=0.3432) in patients with L858R (n=138).

The PFS benefit of GIOTRIF was accompanied by improvement in disease-related symptoms, as measured by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaires (QLQ-C30 and QLQ-LC13). GIOTRIF statistically significantly delayed the time to deterioration for the pre-specified symptoms of cough (HR 0.453; 95% CI 0.299, 0.685; p = 0.0001), dyspnoea (HR 0.536; 95% CI 0.395, 0.727; p <0.0001), and pain (HR 0.703; 95% CI 0.514, 0.961; p = 0.0265) compared with chemotherapy. Significantly more patients treated with GIOTRIF compared with chemotherapy had improvements for cough (75.9% of patients vs.

55.4%; p=0.0003), dyspnoea (70.9% vs. 47.5%; p <0.0001), and pain (64.3% vs. 46.5%; p=0.0029).
Mean scores over time for health-related quality of life (HRQoL) were measured using the EORTC QLQ-C30. Mean scores over time for overall quality of life, global health status and physical, role, cognitive, social and emotional functioning were significantly favouring GIOTRIF® over chemotherapy.

LUX-Lung 2 (1200.22)

LUX-Lung 2 was an open label single arm Phase II trial which investigated the efficacy and safety of GIOTRIF in 129 EGFR TKI-naïve patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations. Patients were enrolled in the first-line (N=61) or second-line setting (N=68) (i.e. after failure of 1 prior chemotherapy regimen). Patients were centrally screened for EGFR mutations.
The primary endpoint was ORR. Secondary endpoints included PFS, DCR and OS.
In 61 patients treated in the first-line setting, confirmed ORR was 65.6% and DCR was 86.9% according to independent review. The median PFS was 12.0 months by independent review and 15.6 months by investigator assessment. Median OS was not reached in the first-line population. Efficacy was similarly high in the group of patients who had received prior chemotherapy (N=68; ORR 57.4%; PFS by independent review 8 months and by investigator assessment 10.5 months; DCR 77.9%). Median OS in the second line patients was 23.3 months (95% CI 18.5-38).

Analysis of GIOTRIF's efficacy in EGFR TKI naïve patients with tumours harbouring uncommon EGFR Mutations (LUX-Lung 2, -3 and -6)

In three clinical trials of GIOTRIF® with prospective tumour genotyping (Phase 3 trials LUX-Lung 3 and -6, and single arm Phase 2 trial LUX-Lung 2), an analysis was conducted of data from a total of 75 TKI-naive patients with advance (stage III-b-IV) lung adenocarcinomas harbouring uncommon EGFR mutations, which were defined as all mutations other than Del 19 and L858R mutations. Patients were treated with GIOTRIF® 40 mg (all three trials) or 50 mg (LUX-Lung 2) orally once daily.

In patients with tumours harbouring either G719X (N=18), L861Q (N=16), or S768I substitution mutation (N=8), the confirmed ORR was 72.2%, 56.3 %, 75.0%, respectively, and the median duration of response was 13.2 months, 12.9 months and 26.3 months, respectively.

In patients with tumours harbouring exon 20 insertions (N=32) the confirmed ORR was 8.7% and the median duration of response was 7.1 months. In patients with tumours harbouring de-novo T790M mutations (N=14) the confirmed ORR was 14.3% and the median duration of the response was 8.3 months.

LUX-Lung 7 (1200.123)

LUX-Lung 7 is a randomized, global, open label Phase IIb trial investigating the efficacy and safety of GIOTRIF in patients with locally advanced or metastatic lung adenocarcinoma (stage IIIB or IV) with EGFR mutations in the first-line setting. Patients were screened for the presence of activating EGFR mutations (Del 19 and/or L858R) using the TheraScreen EGFR RGQ PCR Kit, Qiagen Manchester Ltd. Patients (N=319) were randomised (1;1) to receive GIOTRIF 40 mg orally twice once daily (N=160) or gefitinib 250 mg orally once daily (N=159). Randomisation was stratified according to EGFR mutations (Del 19; L858R) and presence of brain metastases (yes; no).

Among the patients randomized, 62% were female, the median age was 63 years, 16% of patients had brain metastases, the baseline ECOG performance status was 0 (31%) or 1 (69%), 57% were Asian and 43% were non-Asian. Patients had a tumour sample with an EGFR mutation categorized as either exon 19 deletion (58%) or exon 21 L858R substitutions (42%).

The co-primary endpoints are PFS by independent review, time to treatment failure (TTF) and OS. Secondary endpoints include ORR and DCR. The risk of progression was significantly reduced for afatinib versus gefitinib (see Table 9) and ORR was 70% for afatinib and 56% for gefitinib. Primary analysis of OS will be conducted after the number of required events has occurred as per protocol.

Table 9 Efficacy results of GIOTRIF vs. gefitinib (LUX-Lung 7 Trial) based on primary analysis as of August 2015

	GIOTRIF (N = 160)	Gefitinib (N = 159)	Hazard Ratio/ Odds Ratio (95% CI) p-value[2]
Median PFS (months) Overall Trial Population	11.0	10.9	HR 0.73 (0.57-0.95) 0.0165
18-months PFS rate	27%	15%	
24-months PFS rate	18%	8%	
Median OS (months)[1] Overall Trial Population	27.9	25.0	HR 0.87 (0.65, 1.15) 0.33

[1]OS analysis immature as of August 2015
[2]p-value for PFS/TTF/OS based on stratified log-rank test

A statistically significant improvement in TTF was observed for patients treated with GIOTRIF® in comparison the those treated with gefitinib, hazard ratio 0.73 (95% CI [0.58-0.92]; p=0.0073), with median TTF values of 13.7 and 11.5 months, respectively. The percentage of GIOTRIF patients still on treatment after 18 and 24 months was 35% and 25% in comparison to 27% and 13% for gefitinib treated patients.

The PFS hazard ration for patients with DEL 19 mutations and L858R mutations was 0.76 (95% CI [0.55, 1.06]; p=0.1071, and 0.71 (95% CI [0.47, 1.06]; p=0.08560 respectively for afatinib vs gefitinib.

Time to Treatment Failure (TTF)

Time to Treatment Failure (TTF), is defined as the time (months) from the date of randomisation to the date of permanent treatment discontinuation for any reason. Patients still receiving study treatment at the time of the analysis were censored at the date of their last known administration of study treatment.

At the time of the data cut-off for the primary analysis, 140 patients (87.5%) in the afatinib arm and 149 patients (93.7%) in the gefitinib arm had permanently discontinued treatment with trial medication. Treatment with afatinib reduced the risk for treatment failure by 27.2% compared with treatment with gefitinib; the HR was significant at the nominal alpha-level of 5% (HR 0.728; 95% CI 0.576, 0.920; p=0.0073). Median TTF was 13.67 months in the afatinib arm and 11.53 months in the gefitinib arm. The analysis of TTF is summarised in Table 10 and 11.

Table 10 Time to Treatment Failure (TTF)

	GIOTRIF (N = 160)	Gefitinib (N = 159)	Hazard Ratio/ Odds Ratio (95% CI) p-value[1]
Time to Treatment Failure (months)	13.7	11.5	HR 0.73 (0.58-0.92) 0.0073
18-months PFS rate	35%	27%	
24-months PFS rate	25%	13%	

[1]p-value for PFS/TTF/OS based on stratified log-rank test

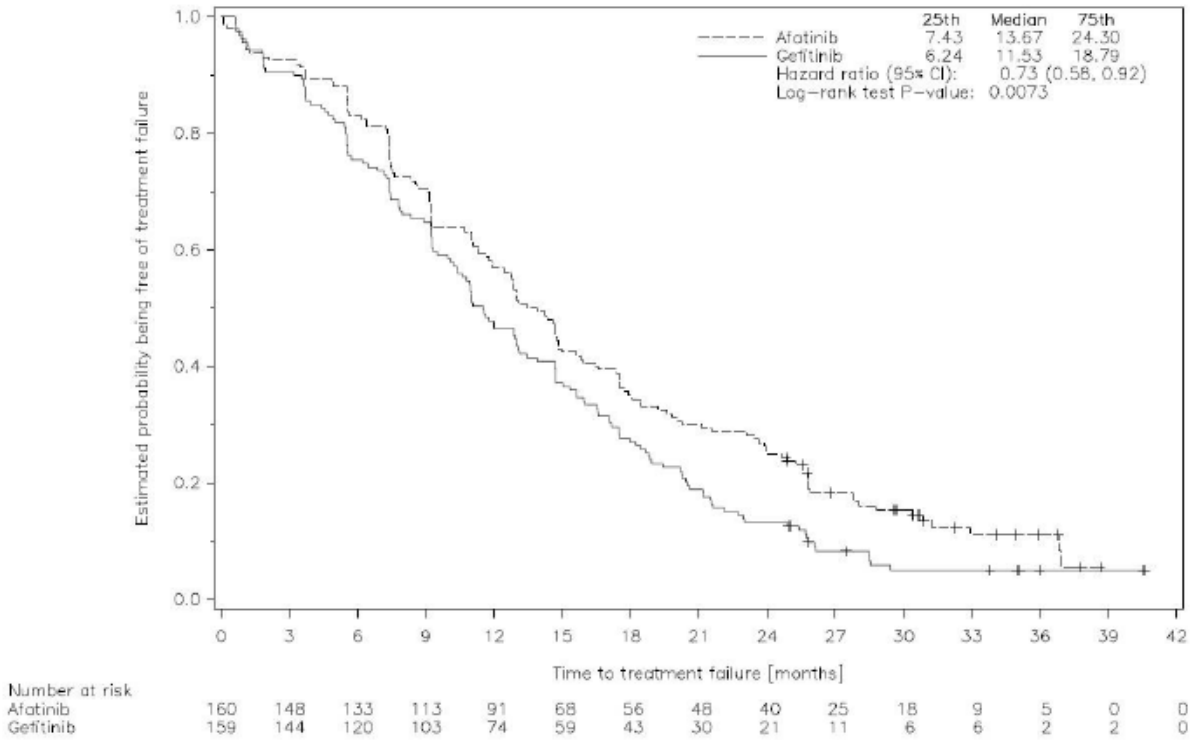
Table 11 Time to Treatment Failure / RS

	Afatinib	Gefitinib
Patients [N (%)]	160 (100.0)	159 (100.0)
Patients with treatment failure [N (%)]	140 (87.5)	149 (93.7)
Time to treatment failure [months]		
25th percentile (95% CI)	7.43 (6.37, 9.17)	6.24 (5.03, 7.82)
Median (95% CI)	13.67 (11.89, 14.95)	11.53 (10.09, 13.11)
75th percentile (95% CI)	24.30 (19.61, 25.86)	18.79 (16.56, 21.16)
Hazard ration vs. gefitinib[1]	0.728	
95% CI	(0.576, 0.920)	
p-value (2-sided)[2]	0.0073	

[1] Hazard ratio derived using a Cox proportional hazard model stratified by EGFR mutation group and presence of brain metastases
[2] Derived using a log-rank test stratified by EGFR mutation group and presence of brain metastases

At 12 months, the probabilities of still being on treatment were 56.9% for patients in the afatinib arm and 46.5% for patients in the gefitinib arm (at 18 months: 35.0% vs. 27.0%; at 24 months: 25.0% vs. 13.2%). The corresponding Kaplan-Meier curves are displayed in Figure 3.

Figure 3 Kaplan-Meier curves for Probability of Time to Treatment Failure



GIOTRIF in patients with NSCLC of squamous histology

LUX-Lung 8 (1200.125)

The efficacy and safety of GIOTRIF as second-line treatment for patients with advanced NSCLC of squamous histology was investigated in a randomized open-label global Phase III trial LUX-Lung 8. Patients who received at least 4 cycles of platinum-based therapy in the first line setting were subsequently randomized 1:1 to daily GIOTRIF 40 mg or erlotinib 150 mg until progression. Dose escalation of GIOTRIF to 50 mg was allowed after first cycle (28 days) on treatment in case of no or limited drug related adverse events (i.e. absence of diarrhoea, skin rash, stomatitis, and/or other drug related events above CTCAE Grade 1), compliant dosing and no prior dose reduction. Randomization was stratified by race (Eastern Asian vs non Eastern Asian). The primary endpoint was PFS (analysed when at least 372 events were reported by independent

review) using RECIST v. 1.1. OS was the key secondary endpoint (analysed at first 632 deaths). Other secondary endpoints included ORR, and HRQOL.

Overall 795 patients were randomized. The median age of patients in the trial was 64.0 years; 83.8% of patients were male, 72.8% were White, and 21.6% were Eastern Asian. Of the 91.6% who were classified as "other current or ex-smokers", 19.6% were current smokers. At the time of screening 32.7% of patients had an ECOG performance score of 0 and 66.8% had a score of 1.

Almost all patients (99.4%) had Stage IIIB (12.1%) or IV (87.3%) disease at screening. Overall, 3.5% of patients were reported to have a histologic sub classification of mixed and 0.5% had histologic sub classification of undifferentiated. The remainder (96.0%) of patients had a histologic sub classification reported as squamous only.

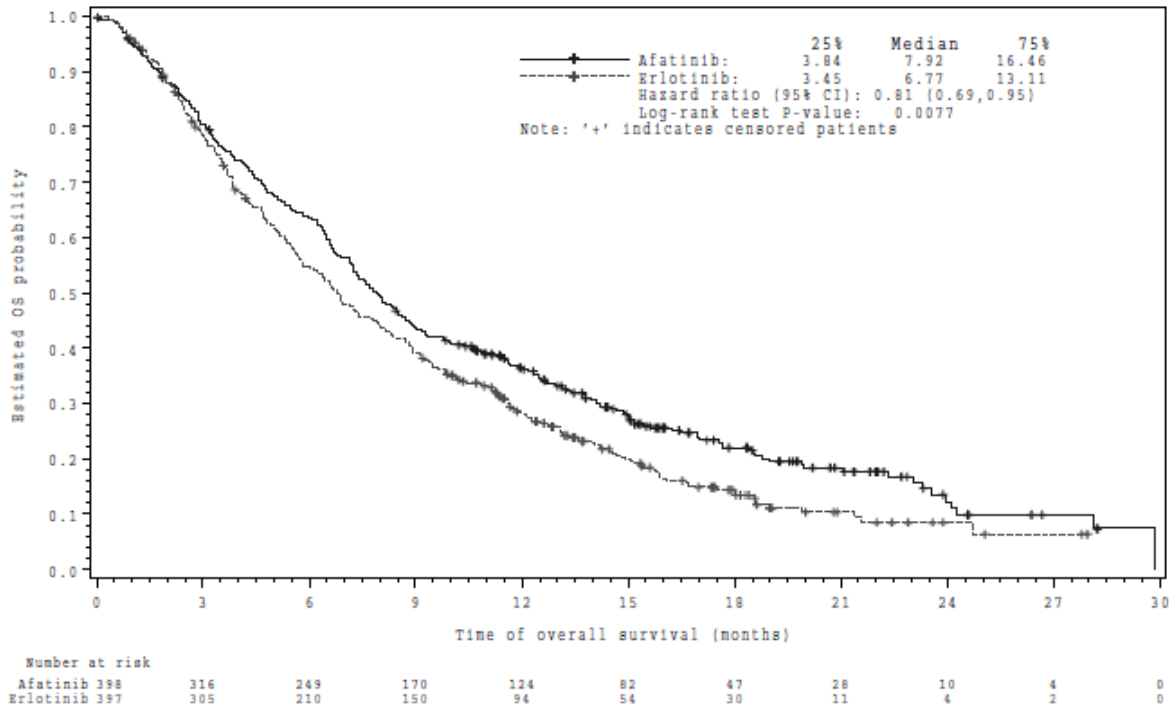
The study demonstrated that second-line GIOTRIF resulted statistically significant improvement in PFS and OS of patients with squamous NSCLC compared to erlotinib. In the primary PFS analysis median PFS was 2.43 months in the GIOTRIF group and 1.94 months on erlotinib (HR=0.82, 95% CI (0.676, 0.998), p=0.0427). The final PFS analysis including all randomized patients confirmed earlier results (Table 12). The primary analysis of OS demonstrated significant reduction in the risk of death for patients treated with GIOTRIF compared with erlotinib (HR=0.81 95% CI (0.69, 0.95), p=0.0077).

Table 12 Efficacy results for GIOTRIF vs erlotinib in LUX-Lung 8, based on primary analysis of OS, including patients all randomized

	GIOTRIF (N=398)	**Erlotinib (n=397)**	**Hazard Ratio/ Odds Ratio (95%CI)**	**p value[2]**
PFS Months (median)	2.63	1.94	HR 0.81 (0.69, 0.96)	0.0103
OS Months (median)	7.92	6.77	HR 0.81 (0.69, 0.95)	0.0077
Alive at 12 months	36.4%	28.2%		
Alive at 18 months	22.0%	14.4%		
Objective Response Rate (CR+PR)[1]	5.5%	2.8%	OR 2.06 (0.98, 4.32)	0.0551
Duration of response Months (median)	7.29	3.71		

[1]CR=complete response; PR=partial response
[2]p-value for PFS/OS based on stratified log-rank test; p-value for Objective Response Rate based on logistic regression

Figure 4 Kaplan-Meier Curve for overall survival/randomized set



The pre-specified HRQoL endpoints were symptoms of cough, dyspnea, and pain as well as global health status/HRQoL as measured by the EORTC QLQ-C30 and QLQ-LC13 questionnaires. Afatinib and erlotinib treatment were compared in terms of the proportion of patients with a status change, time to deterioration, and changes in scores over time. On treatment completion rate of questionnaires ranged between 69% and 99%. Significantly more patients in the GIOTRIF group reported improvement in the global health status / quality of life compared to erlotinib (35.7% vs 28.3%, p=0.0406). Higher proportion of GIOTRIF patients had improvement in cough (43.4% vs 35.2%, p=0.0294) and dyspnea (51.3% vs 44.1%, p=0.0605), while no differences was observed for pain (40.2% vs 39.2%, p=0.7752). GIOTRIF significantly delayed time to deterioration of dyspnea (HR 0.79, p=0.0078). GIOTRIF significantly delayed time deterioration of dyspnea versus erlotinib; 2.63 months vs. 1.91 months, respectively. Median time to deterioration of cough was 4.53 months with afatinib and 3.65 months with erlotinib (HR 0.89, p=0.2562); no difference was observed for time to deterioration of pain (HR 0.99, p=0.8690). The time to deterioration of diarrhea and sore mouth was significantly shorter in the afatinib arm (HR 1.81 and 1.59, respectively). A higher number of patients reported dysphagia in the afatinib arm compared to erlotinib (HR 1.12). Mean scores over time for cough, dyspnea, and pain, as well as for physical, role, cognitive, and emotional functioning, were significantly better for GIOTRIF then for erlotinib. Mean scores over time were significantly worse for diarrhea, sore mouth and dysphagia for afatinib compared to erlotinib. There were no differences between afatinib and erlotinib for changes in global health score/HRQoL over time.

Pharmacokinetics

Absorption and distribution

Following oral administration of GIOTRIF , maximum concentrations (C_{max}) of afatinib are observed approximately 2 to 5 hours post dose. Mean C_{max} and $AUC_{0-\infty}$ values increased slightly more than proportional in the dose range from 20 mg to 50 mg GIOTRIF. Systemic exposure to afatinib is decreased by 50% (C_{max}) and 39% ($AUC_{0-\infty}$), when administered with a high-fat meal compared with administration in the fasted state. Based on population pharmacokinetic data derived from clinical trials in various tumour types, an average decrease of 26% in $AUC_{\tau,ss}$ was observed when food was consumed within 3 hours before or 1 hour after taking GIOTRIF. Therefore, food should not be consumed for at least 3 hours before and at least 1 hour after taking GIOTRIF (see sections "Dosage and Administration" and "Interactions"). After administration of GIOTRIF, the mean relative bioavailability was 92% (adjusted gMean ratio of $AUC_{0-\infty}$) when compared to an oral solution.

In vitro binding of afatinib to human plasma proteins is approximately 95%.

The volume of distribution was 1940 L for single dose treatment and 2770 L at steady state. The absolute bioavailability of GIOTRIF is unknown.

Metabolism and excretion

Enzyme-catalyzed metabolic reactions play a negligible role for afatinib *in vivo*. Covalent adducts to proteins are the major circulating metabolites of afatinib.

Following administration of an oral solution of 15 mg afatinib, 85.4% of the dose was recovered in the faeces and 4.3% in urine. The parent compound afatinib accounted for 88% of the recovered dose. The apparent terminal half-life is 37 hours. Steady state plasma concentrations of afatinib are achieved within 8 days of multiple dosing of afatinib resulting in an accumulation of 2.77-fold (AUC) and 2.11-fold (C_{max}).

Renal impairment

Less than 5% of a single dose of afatinib is excreted via the kidneys.

Exposure to Afatinib in subjects with renal impairment was compared to healthy volunteers following a single dose of 40 mg GIOTRIF. Subjects with moderate renal impairment (n=8, eGFR 30-59 mL/min, according to the Modification of Diet in Renal Disease [MDRD] formula) had an exposure of 101% (C_{max}) and 122% (AUC_{0-tz}) in comparison to their healthy controls. Subjects with severe renal impairment (n=8; eGFR 15-29 mL/min, according to the MDRD formula) had an exposure of 122% (C_{max}) and 150% (AUC_{0-tz}) in comparison to their healthy controls. Based on this trial and population pharmacokinetic analysis of data derived from clinical trials in various tumour types, it is concluded, that adjustments to the starting dose in patients with mild (eGFR 60-89 mL/min) and moderate (eGFR 30-59 mL/min) renal impairment are not necessary, but patients with severe impairment (eGFR 15-29 mL/min) administer Giotrif at starting dose of 30 mg once daily. Monitor patients with severe renal impairment and adjust GIOTRIF dose if not tolerated (see sections "Population pharmacokinetic analysis in special populations" below and "Dosage and Administration"). GIOTRIF has not been studied in patients with eGFR <15 mL/min or on dialysis.

Hepatic impairment

Afatinib is eliminated mainly by biliary/faecal excretion. Subjects with mild (Child Pugh A) or moderate (Child Pugh B) hepatic impairment had similar exposure in comparison to healthy volunteers following a single dose of 50 mg GIOTRIF. This is consistent with

population pharmacokinetic data derived from clinical trials in various tumour types (see section "Population pharmacokinetic analysis in special populations" below). No starting dose adjustments appear necessary in patients with mild or moderate hepatic impairment (see section "Dosage and Administration"). The pharmacokinetics of afatinib had not been studied in subjects with severe (Child Pugh C) hepatic dysfunction (see "Special warnings and precautions").

Population pharmacokinetic analysis in special populations

A population pharmacokinetic analysis was performed in 927 cancer patients (764 with NSCLC) receiving GIOTRIF monotherapy. No starting dose adjustment is considered necessary for any of the following covariates tested.

Age
No significant impact of age (range: 28-87 years) on the pharmacokinetics of afatinib could be observed.

Body weight
Plasma exposure ($AUC_{\tau,ss}$) was increased by 26% for a 42 kg patient (2.5th percentile) and decreased by 22% for a 95 kg patient (97.5th percentile) relative to a patient weighing 62 kg (median body weight of patients in the overall patient population).

Gender
Female patients had a 15% higher plasma exposure ($AUC_{\tau,ss}$, body weight corrected) than male patients.

Race
There was no statistically significant difference in afatinib pharmacokinetics between Asian and Caucasian patients. Also no obvious difference in pharmacokinetics for American Indian/ Alaska native or Black patients could be detected based on the limited data available in these populations (6 and 9 out of 927 patients included in the analysis, respectively).

Renal impairment
Exposure to GIOTRIF moderately increased with lowering the creatinine clearance (CrCL), i.e. for a patient with a CrCL of 60 or 30 mL/min exposure ($AUC_{\tau,ss}$) to afatinib increased by 13% and 42%, respectively, and decreased by 6% and 20% for a patient with CrCL of 90 or 120 mL/min, respectively, compared to a patient with the CrCL of 79 mL/min (median CrCL of patients in the overall patient population analysed).

Hepatic impairment
Patients with mild and moderate hepatic impairment as identified by abnormal liver tests did not correlate with any significant change in afatinib exposure.

Other patient characteristics/intrinsic factors
Other patient characteristics/intrinsic factors found with a significant impact on afatinib exposure were: ECOG performance score, lactate dehydrogenase levels, alkaline phosphatase levels and total protein. The individual effect sizes of these covariates were considered not clinically relevant.

Smoking history, alcohol consumption, or presence of liver metastases had no significant impact on the pharmacokinetics of afatinib.

Pharmacokinetic Drug Interactions

Drug transporters:

P-glycoprotein (P-gp)

Effect of P-gp inhibitors and inducers on afatinib
Two trials were conducted to assess the effect of ritonavir, a potent inhibitor of P-gp, on the pharmacokinetics of afatinib. In one trial, the relative bioavailability of afatinib was investigated when ritonavir (200 mg b.i.d. for 3 days) was given either simultaneously or 6 hours after a single dose of 40 mg GIOTRIF. The relative bioavailability of afatinib was 119% ($AUC_{0-\infty}$) and 104% (C_{max}) when administered simultaneously with ritonavir and 111% ($AUC_{0-\infty}$) and 105% (C_{max}) when ritonavir was administered 6 hours after GIOTRIF. In a second trial, when ritonavir (200 mg b.i.d. for 3 days) was administered 1 hour before a single dose of 20 mg GIOTRIF, exposure to afatinib increased by 48% ($AUC_{0-\infty}$) and 39% (C_{max}) (see sections "Dosage and Administration", "Special Warnings and Precautions", and "Interactions").

Pre-treatment with rifampicin (600 mg q.d. for 7 days), a potent inducer of P-gp, decreased the plasma exposure to afatinib by 34% ($AUC_{0-\infty}$) and 22% (C_{max}) after administration of a single dose of 40 mg GIOTRIF (see sections "Special Warnings and Precautions" and "Interactions").

Effect of afatinib on P-gp Substrates
Based on *in vitro* data, afatinib is a moderate inhibitor of P-gp. It is considered unlikely that GIOTRIF treatment will result in changes of the plasma concentrations of other P-gp substrates.

Breast cancer resistance protein (BCRP)

In vitro studies indicated that afatinib is a substrate and an inhibitor of the transporter BCRP.

Drug Uptake Transport Systems

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of OATB1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and OCT3 transporters are considered unlikely.

Drug metabolising enzymes:

Cytochrome P450 (CYP) enzymes

Effect of CYP enzymes inducers and inhibitors on afatinib
In vitro data indicated that drug-drug interactions with afatinib due to inhibition or induction of CYP enzymes by concomitant medicines are considered unlikely. In

humans it was found that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib. Approximately 2% of the afatinib dose was metabolized by FMO3 and the CYP3A4-dependent N-demethylation was too low to be quantitatively detected.

Effect of afatinib on CYP enzymes
Afatinib is not an inhibitor or an inducer of CYP enzymes. Therefore, GIOTRIF is unlikely to affect the metabolism of other medicines that are dependent on CYP enzymes.

UDP-glucuronosyltransferase 1A1 (UGT1A1)

In vitro data indicated that drug-drug interactions with afatinib due to inhibition of UGT1A1 are considered unlikely.

Pharmacodynamics

Cardiac Electrophysiology
GIOTRIF at doses of 50 mg daily did not result in significant prolongation of the QTcF interval after single and multiple administrations in patients with relapsed or refractory solid tumours. There were no cardiac safety findings of clinical concern. This suggest that GIOTRIF does not have a relevant effect on the QTcF interval.

Toxicology

Oral administration of single doses to mice and rats indicated a low acute toxic potential of afatinib. In oral repeated-dose studies for up to 26 weeks in rats or 52 weeks in minipigs the main effects were identified in the skin (dermal changes, epithelial atrophy and folliculitis in rats), the gastrointestinal tract (diarrhoea, erosions in the stomach, epithelial atrophy in rats and minipigs) and the kidneys (papillary necrosis in rats). Depending on the finding, these changes occurred at exposures below, in the range of or above clinically relevant levels. Additionally, in various organs pharmacodynamically mediated atrophy of epithelia was observed in both species.

Reproduction toxicity
Based on the mechanism of action, GIOTRIF has the potential to cause foetal harm. The embryo-foetal development studies performed on afatinib revealed no indication of teratogenicity up to dose levels including maternal death. Changes identified were restricted to skeletal alterations consisting of incomplete ossifications/unossified elements (rat) and abortions at maternally toxic dose, reduced foetal weights as well as mainly visceral and dermal variations (rabbit). The respective total systemic exposure (AUC) was either slightly above (2.2 times in rats) or below (0.3 times in rabbits) compared with levels in patients.

Radiolabelled afatinib administered orally to pregnant rats on Day 11 of lactation was excreted into milk of the dams. The average concentrations in milk at time points 1 h and 6 h post dose were approximately 80- and 150-fold above the respective concentration in plasma.

A fertility study in male and female rats by the oral route up to the maximum tolerated dose revealed no significant impact on fertility. The total systemic exposure (AUC_{0-24}) that

could be achieved in male and female rats was in the range or less than that observed in patients (1.3 times and 0.51 times, respectively).
A study in rats by the oral route up to the maximum tolerated doses revealed no significant impact on pre-/postnatal development. Effects were limited to lower birth weight and body weight gain of offspring but without materially affecting the attainment of developmental landmarks, sexual maturation or performance with behavioural assessments. The highest total systemic exposure (AUC_{0-24}) that could be achieved in female rats was less than that observed in patients (0.23 times).

Phototoxicity
An *in vitro* 3T3 phototoxicity test with afatinib was performed. It was concluded that GIOTRIF may have phototoxicity potential.

Carcinogenicity
Carcinogenicity studies have not been conducted with Afatinib.
A marginal response to afatinib was observed in a single tester strain of a bacterial (Ames) mutagenicity assay. However, no mutagenic or genotoxic potential could be identified in an *in vitro* chromosomal aberration test at non-cytotoxic concentrations as well as the *in vivo* bone marrow micronucleus assay, the *in vivo* Comet assay and an *in vivo* 4-week oral mutation study in the Muta™ Mouse.

Availabilty

Film coated-tablets 20 mg Box, 4 Pouch @ 1 Alublister @ 7 film-coated tablets	Reg. No. DKI1552503117A1
Film coated-tablets 30 mg Box, 4 Pouch @ 1 Alublister @ 7 film-coated tablets	Reg. No. DKI1552503117B1
Film coated-tablets 40 mg Box, 4 Pouch @ 1 Alublister @ 7 film-coated tablets	Reg. No. DKI1552503117C1

Storage Conditions:
Store in the original package in order to protect from moisture and light
Store below 30°C, in a safe place, out of the reach of children

Only on doctor's prescription
Harus dengan resep dokter

Manufactured by:
Boehringer Ingelheim Pharma GmbH & Co.KG
Ingelheim am Rhein, Germany

For:
Boehringer Ingelheim International GmbH
Ingelheim am Rhein, Germany

Imported by:
PT Boehringer Ingelheim Indonesia
Bogor, Indonesia

Produk Informasi untuk Pasien

GIOTRIF
(Afatinib)
tablet

Bacalah informasi ini sebelum anda mulai menggunakan GIOTRIF dan setiap kali anda mendapatkan resepnya. Mungkin saja terdapat informasi baru. Informasi ini tidak menggantikan konsultasi anda dengan dokter mengenai kondisi atau pengobatan medis anda.

Apakah GIOTRIF?
GIOTRIF adalah obat resep yang digunakan untuk mengobati pasien dengan kanker paru jenis karsinoma bukan sel kecil (KPKBSK), yang memiliki gen *epidermal growth factor receptor* (EGFR) abnormal tipe tertentu, dan belum pernah diobati untuk kanker yang telah menyebar ke bagian tubuh lainnya. Belum diketahui apakah GIOTRIF aman dan efektif untuk anak.

Obat ini digunakan untuk mengobati pasien dewasa dengan tipe kanker yang spesifik di paru-paru (karsinoma bukan sel kecil (KPKBSK));
- Yang diidentifikasikan dengan mutasi di gen EGFR. Giotrif dapat diresepkan pada Anda apabila sebelumnya Anda belum pernah diberikan obat golongan Inhibitor Tirosin Kinase
- Tipe *squamous* jika kemoterapi sebelumnya tidak mencukupi

Apa yang harus saya beritahukan kepada dokter sebelum menggunakan GIOTRIF?
Sebelum anda menggunakan GIOTRIF, beritahukan kepada dokter anda bila anda:
- Memiliki masalah ginjal atau hati.
- Memiliki masalah paru atau pernapasan lainnya disamping kanker paru.
- Memiliki riwayat mata kering berat atau masalah mata lainnya. Beritahukan kepada dokter anda bila anda menggunakan lensa kontak.
- Memiliki masalah jantung.
- Memiliki kondisi medis lainnya.
- Sedang hamil atau merencanakan untuk hamil. GIOTRIF dapat membahayakan bayi anda yang belum dilahirkan. Anda sebaiknya tidak hamil ketika menggunakan GIOTRIF. Perempuan usia subur sebaiknya menggunakan kontrasepsi yang efektif selama pengobatan dengan GIOTRIF dan paling sedikit 2 minggu setelah penggunaan dosis terakhir GIOTRIF. Bicarakan kepada dokter anda mengenai metode kontrasepsi yang tepat bagi anda. Beritahukan segera kepada dokter anda bila anda hamil ketika menggunakan GIOTRIF.
- Sedang menyusui atau merencanakan untuk menyusui. Belum diketahui apakah GIOTRIF dapat masuk kedalam air susu ibu. Anda dan dokter anda sebaiknya memutuskan apakah anda akan menggunakan GIOTRIF atau menyusui. Anda sebaiknya tidak melakukan kedua hal tersebut bersama-sama.
- Beritahukan kepada dokter anda mengenai semua obat yang anda minum, seperti obat resep dan obat bebas, vitamin, dan suplemen herbal. GIOTRIF dapat mempengaruhi cara kerja obat lain, dan obat lain juga dapat mempengaruhi cara kerja GIOTRIF.

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- Mengetahui obat yang anda minum. Buatlah daftar obat yang anda gunakan dan perlihatkan kepada dokter atau ahli farmasi anda ketika anda mendapatkan obat baru.

Bagaimanakah cara menggunakan GIOTRIF?
Gunakan GIOTRIF dengan tepat sesuai instruksi dokter anda.

Dokter anda akan memberitahukan kepada anda berapa banyak tablet GIOTRIF yang harus anda minum dan kapan anda meminumnya. Jangan mengubah dosis atau menghentikan GIOTRIF kecuali dokter anda yang menyarankannya.

Minum GIOTRIF pada saat lambung kosong paling sedikit 1 jam sebelum makan atau 3 jam setelah makan.

Bila anda terlupa satu dosis GIOTRIF, minumlah segera begitu anda teringat. Bila hal tersebut terjadi dalam 8 jam sebelum dosis selanjutnya, lewatkan dosis obat yang terlupa dan kemudian minumlah dosis obat selanjutnya sesuai jadwal.

Jangan minum 2 dosis GIOTRIF pada saat yang sama.

Bila anda minum terlalu banyak GIOTRIF, hubungi dokter anda atau pergilah segera ke unit gawat darurat rumah sakit terdekat.

Apakah yang sebaiknya saya hindari ketika menggunakan GIOTRIF?
Batasi waktu pajan anda dengan sinar matahari. GIOTRIF dapat membuat kulit anda sensitif terhadap sinar matahari. Anda dapat mengalami kejadian baru atau perburukan kejadian ruam atau jerawat. Anda dapat mengalami kulit terbakar sinar matahari derajat berat. Gunakan tabir surya dan pakailah topi dan baju yang menutupi kulit anda ketika anda menggunakan GIOTRIF dan apabila anda harus terpajan sinar matahari.

Apakah kemungkinan efek samping GIOTRIF?
GIOTRIF dapat menyebabkan efek samping yang serius, seperti:
- Diare. Diare sering terjadi pada pasien yang menggunakan GIOTRIF dan kadang dapat menjadi berat. Diare berat dapat menyebabkan hilangnya cairan tubuh (dehidrasi) dan masalah ginjal yang kadang dapat menyebabkan kematian. Selama pengobatan dengan GIOTRIF, dokter anda sebaiknya meresepkan obat diare. Gunakan obat ini dengan tepat sesuai instruksi dokter anda. Beritahukan kepada dokter anda bila anda mengalami diare. Dapatkan perawatan medis segera bila diare anda tidak segera sembuh atau bertambah berat.
- Reaksi kulit. GIOTRIF dapat menyebabkan kulit merah, ruam dan jerawat. Penting bagi anda untuk mendapatkan pengobatan segera untuk reaksi kulit tersebut begitu anda mengetahuinya. Minumlah obat untuk membantu mengatasi reaksi kulit anda dengan tepat sesuai instruksi dokter anda. Dapatkan perawatan medis segera bila anda mengalami reaksi kulit berat seperti kulit terkelupas atau melepuh.
- Masalah paru atau pernapasan. Beritahukan segera kepada dokter anda bila anda mengalami gangguan paru yang baru saja terjadi atau perburukan dari penyakit paru anda, atau kombinasi gejala berikut ini:
    - Kesulitan bernapas atau sesak napas
    - Batuk
    - Demam

- Masalah hati. Beritahukan segera kepada dokter anda bila anda mengalami gejala gangguan hati seperti:
    - Kulit atau bagian putih mata anda menjadi menguning (jaundis)
    - Urin berwarna gelap atau coklat (berwarna seperti teh)
    - Nyeri pada bagian kanan atas perut (abdomen)
    - Lebih mudah mengalami pendarahan atau memar dibandingkan normal
    - Merasa sangat lelah

  Dokter anda akan melakukan tes darah untuk mengecek fungsi hati anda selama pengobatan dengan GIOTRIF.
- Masalah mata. Beritahukan segera kepada dokter anda bila anda mengalami gejala gangguan mata seperti:
    - Mata nyeri, bengkak, merah, atau berair
    - Penglihatan buram
    - Sensitif terhadap cahaya
    - Perubahan penglihatan lainnya
- Masalah jantung. Beritahukan segera kepada dokter anda bila anda mengalami gejala penyakit jantung seperti:
    - Sesak napas yang baru saja terjadi atau sesak napas memberat ketika istirahat atau setelah aktivitas
    - Batuk
    - Lelah
    - Bengkak pada mata kaki, telapak kaki atau tungkai
    - Merasakan jantung berdebar atau berdetak cepat (palpitasi)
    - Berat badan meningkat tiba-tiba

Efek samping yang paling sering terjadi akibat GIOTRIF adalah:
- diare
- ruam
- sariawan
- infeksi kuku
- kulit kering
- jerawat
- menurunnya nafsu makan
- gatal

Beritahukan kepada dokter anda bila anda mengalami efek samping apapun yang mengganggu anda atau yang tidak segera sembuh.

Efek samping tersebut diatas belum meliputi seluruh kemungkinan efek samping dari GIOTRIF. Untuk informasi lebih lanjut, tanyakan kepada dokter atau ahli farmasi anda.

Hubungi dokter anda untuk mendapatkan saran medis dari efek samping obat. Anda dapat melaporkan efek samping kepada Badan Pengawas Obat dan Makanan.

Bagaimana cara menyimpan GIOTRIF?
Simpan GIOTRIF pada suhu ruangan dibawah 30°C.
Biarkan GIOTRIF dalam kotak aslinya dan pastikan kotak tersebut tertutup rapat.
Jauhkan GIOTRIF dari lembab dan cahaya.
GIOTRIF yang kadaluarsa atau tidak dibutuhkan lagi sebaiknya dibuang dengan cara yang aman.

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Jauhkan GIOTRIF dan seluruh obat lainnya dari jangkauan anak-anak.

Informasi umum mengenai GIOTRIF
Obat-obatan kadangkala diresepkan untuk tujuan lain dari yang tertulis dalam leaflet Informasi bagi pasien. Jangan gunakan GIOTRIF untuk kondisi selain dari yang diresepkan. Jangan berikan GIOTRIF kepada orang lain walau mereka memiliki gejala yang sama dengan anda. Obat ini dapat membahayakan mereka.

Informasi bagi pasien ini merupakan ringkasan informasi yang paling penting mengenai GIOTRIF. Bila anda menginginkan lebih banyak informasi mengenai GIOTRIF, bicaralah kepada dokter anda. Anda dapat bertanya kepada dokter atau ahli farmasi anda mengenai GIOTRIF yang dituliskan untuk profesional kesehatan.

Apakah bahan yang terkandung dalam GIOTRIF?

Bahan aktif: afatinib
Bahan tidak aktif:
- Inti tablet: laktosa monohidrat, mikrokristalin selulosa, koloidal silikon dioksida, krospovidon, magnesium stearat.
- Selaput tablet: hipromelosa, makrogol 400, titanium dioksida, talk, polisorbat 80, pewarna : Indigo Carmine Aluminum Lake (hanya tablet 30 mg, dan 40 mg).

Leaflet Informasi bagi Pasien ini telah disetujui oleh Badan Pengawas Obat dan Makanan.

Diproduksi oleh:
Boehringer Ingelheim Pharma GmbH & Co. KG
Ingelheim am Rhein, Germany

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